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iREVIEWS

STATE-OF-THE-ART PAPER

Stress Myocardial CT Perfusion

An Update and Future Perspective

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Coronary computed tomography angiography (CTA) has been shown by several multicenter trials to have excellent diagnostic accuracy in the detection and exclusion of significant coronary stenosis. However, a major limitation of coronary CTA is that the physiological significance of stenotic lesions identified is often unknown. Stress myocardial computed tomography perfusion (CTP) is a novel examination that provides both anatomic and physiological information (i.e., myocardial perfusion). Multiple single-center studies have established the feasibility of stress myocardial CTP. Furthermore, it has been illustrated that a combined CTA/CTP protocol improves the diagnostic accuracy to detect hemodynamic significant stenosis as compared with CTA alone; this combined protocol can also be accomplished at a radiation dose comparable to nuclear myocardial perfusion imaging exams. Although initial results hold some promise, stress myocardial CTP is a modality in its infancy. Further research is required to define, validate, and optimize this new technique. However, it is a modality with significant potential, particularly in the evaluation of chest pain patients, given the advantages of short exam time and comprehensive data acquisition. This review highlights how to perform and interpret stress myocardial CTP, summarizes the current literature, and discusses some future directions. (J Am Coll Cardiol Img 2011;4:905–16) © 2011 by the American College of Cardiology Foundation

Recent advances in computed tomography (CT) technology and the rapid evolution of multidetector row CT (1), have allowed cardiac imaging to flourish on this platform. Cardiac CT has been proven to have numerous clinically relevant applications, including coronary artery calcium scoring, coronary computed tomography angiography (CTA), global and regional left ventricular function assessment, and most recently, the assessment of myocardial CT perfusion (CTP) (2–6).

The majority of cardiac CT exams performed today are coronary CTAs, aiming to elucidate the patient's coronary anatomy noninvasively. Coronary CTA has been shown by several multicenter trials to have excellent diagnostic accuracy in the detection and exclusion of significant coronary stenosis (CAD) as compared with invasive coronary angiography (6–8).

Despite its successes, coronary CTA has several inherent limitations restricting its use to a specific population. First and foremost, coronary CTA only provides anatomic information. Many studies have established that functional information is essential in both guiding clinical management and long-term prognosis

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(9–11). The presence of anatomic lesions does not necessarily correlate with functional abnormality—that is, decreased myocardial perfusion (12). Another shortcoming of coronary CTA is its tendency to overestimate the extent of CAD in high-risk patients due to the presence of calcified plaques and stents (13–14).

Given these shortcomings, many attempts have been made to combine coronary CTA with functional studies such as positron emission tomography or single-photon emission computed tomography (SPECT), illustrating complementarity between the techniques (15,16). However, in such scenarios, the patient is required to undergo at least 2 diagnostic studies in order to arrive at the final result, which not only is inconvenient but also subjects the patient to increased radiation exposure. As such, it is evident that a CT-based exam that combines the information provided by anatomy and perfusion, namely stress myocardial computed tomography perfusion (CTP) imaging, can have many potential benefits.

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CTA = computed tomography angiography

CTP = computed tomography perfusion

DECT = dual energy computed tomography

ECG = electrocardiogram

MBF = myocardial blood flow

MDCT = multidetector computed tomography

MPI = myocardial perfusion imaging

NPV = negative predictive value

PPV = positive predictive value

QCA = quantitative coronary angiography

SPECT = single-photon emission computed tomography

Recently, several single-center studies have illustrated the feasibility of stress myocardial CTP and have shown that stress myocardial CTP adds incremental value to traditional coronary CTA in the detection of significant coronary stenosis, potentially overcoming the limitations of coronary CTA alone (17–20). Although initial results hold some promise, stress myocardial CTP is a modality in its infancy, with only a small number of subjects evaluated overall, with no clear optimized protocol as of yet. Further research is required to define, validate, and optimize this technique. However, it is a modality with significant potential, particularly in the evaluation of chest pain patients, given the advantages of short exam time and comprehensive data acquisition. This review will address protocol setup and interpretation of stress myocardial CTP, current literature, and future directions.

Protocol Setup and Interpretation of Stress Myocardial CTP

Overview. Myocardial CTP protocol is composed of a stress phase acquisition and a rest phase acquisition, similar to a nuclear myocardial perfusion imaging (MPI) exam. These acquisitions are evaluated for myocardial perfusion information but also coronary anatomy as well, generally using the rest acquisition. Iodinated contrast is administered both in the stress and rest acquisition (60 to 75 ml for each acquisition), for a total contrast dose of approximately 130 to 150 ml. Stress phase imaging is performed under pharmacological administration of stress agents, such as adenosine, dipyridamole, or regadenoson, similar to nuclear medicine MPI. Additionally, a third optional delayed-phase acquisition can be performed in cases where late contrast enhancement evaluation for myocardial scar is desired.

Patient preparation. In addition to the standard setup of a coronary CTA, myocardial CTP protocol requires a few additional components: namely, 1 additional intravenous catheter if adenosine/dipyridamole infusion is being used, a 12-lead electrocardiogram (ECG) machine, and a blood pressure monitor. Two 18- to 20-gauge intravenous catheters are inserted into the patient's antecubital veins: 1 for the delivery of iodinated contrast material and the other for infusion of the pharmacological stress agent. Actual gauge and site of insertion may vary depending upon the patient's anatomy. Contrast is prepared in a dual-syringe contrast injection system. The pharmacological stress agent is prepared in an infusion pump. Note is made that newer stress agents, such as regadenoson, may require only 1 intravenous site for delivery of the stress agent in a single bolus of 10 s followed by a saline flush. The contrast administration can be given after 1 to 2 min of regadenoson infusion. ECG and blood pressure measurements are performed prior to scan acquisition to establish a baseline for patient monitoring, during and after the procedure is completed.

Choice of stress agents. Although it has been shown in many studies that pharmacological and exercise stress testing have comparable diagnostic characteristics, exercise is the preferred method of stress in myocardial perfusion imaging when possible (21–25). This is due to its physiological mechanism and some reports of greater extent, severity, and reversibility of defects with exercise compared with pharmacological stress (26,27). The main significant limitation of exercise is that many patients, especially in a specific population that would benefit from a stress test, are not able to exercise adequately. Additionally, all published literature on stress myocardial CTP to date has employed pharmacological stress. As such, this review will focus on pharmacological stress agents; however, using exercise stress in myocardial CTP is an area that should be explored in future studies.

Pharmacological stress agents that have been validated via feasibility trials include adenosine and dipyridamole (17–19). Both agents are coronary

vasodilators and work via coronary steal phenomenon where the normal coronary arteries dilate more than their diseased counterpart, leading to a difference in flow in the downstream myocardium and highlighting the perfusion defect in the territory supplied by the diseased artery. Exogenously administered adenosine acts directly on adenosine receptors, causing coronary vasodilation. Dipyridamole increases the level of endogenous adenosine by decreasing the level of reuptake mechanism by endothelial cells (28). Both adenosine and dipyridamole have been shown to have good sensitivity and specificity for the detection of myocardial perfusion defect with stress myocardial CTP. They both have similar side effects profiles that include reflex tachycardia and are similarly contraindicated in patients with asthma, chronic obstructive pulmonary disease, advanced atrioventricular block in the absence of pacemaker, and caffeine use. Adenosine has a short half-life in the seconds and is rapidly removed from the body upon administration. Thus, it has a rapid onset and short duration of action, and continuous infusion is required for the purpose of myocardial CTP. Dipyridamole is also administered using an infusion pump; however, its effects last longer and, unlike adenosine, may require reversal with an adenosine receptor antagonist such as aminophylline. Both agents require weight-based dosing.

Other pharmacological stress agents have been used for stress echocardiograms and nuclear stress MPI but have not been fully validated in studies evaluating myocardial CTP. For example, regadenoson is a selective adenosine receptor agonist, preferentially acting on the A_{2A} receptor, leading to selective coronary vasodilation and, therefore, leading to fewer side effects in patients with reactive airway diseases. Regadenoson is easy to administer, given as a standard dose with no need for weight adjustment, but has a prolonged effect. It may also cause tachycardia, even more so than adenosine. Dobutamine has been utilized mainly in stress echocardiography and works via a more physiological mechanism, by increasing the physiological consumption of oxygen in the myocardium leading to induction of functional abnormalities. Advantages and disadvantages of pharmacological stress agents are summarized in Table 1.

Image acquisition. Scout images are acquired to localize the heart position (Fig. 1). Contrast timing for image acquisition is determined by using a contrast material test bolus of 10 to 15 ml (flow rate: 4 to 5 ml/s) followed by 20 ml of saline flush. The timing is calculated by adding 2 to 4 s to the time of peak contrast enhancement in the ascending aorta, in order to achieve a sufficient level of perfusion of contrast material throughout the myocardium, from the subepicardial to the subendocardial layer and from the base to the apex of the heart. Alternatively, a trigger bolus method may be used where an attenuation-based threshold (Hounsfield unit [HU]) is set at a specific location, for example, 180 HU at the descending aorta, and image acquisition commences once the attenuation is met at that particular location.

There are 2 ways in which to set up a stress and rest myocardial CTP protocol based on the order of scan acquisition, namely, stress phase first followed by rest phase, or vice versa. The main consideration is that the first scan will be a "clean" acquisition, and that the contrast used in the first acquisition can cross-contaminate the second acquisition if the interval between the scans is short (less than approximately 20 to 30 min) (Table 2). When doing a stress phase acquisition first, the detection of myocardial ischemia is optimized by not having

Table 1. Various Stress Agents and Their Advantages/Disadvantages

Agent	Advantage	Disadvantage
Exercise	Physiological Least expensive	Motion → Not validated using MDCT Effort-dependent
Pharmacological		
Adenosine*	Good sensitivity and specificity	Mild tachycardia Contraindicated in patients with COPD, asthma, and caffeine use
Dipyridamole*	Good sensitivity and specificity Inexpensive	Tachycardia May requires aminophylline antagonism Similar contraindications to adenosine
Regadenoson	Easier dosing (10-s bolus) Fewer side effects in patients with COPD and asthma	Prolonged effects Tachycardia
Dobutamine	Physiological mechanism Increase oxygen consumption in the myocardium	Lower sensitivity and specificity for perfusion defects Tachycardia Can provoke ischemia

*Stress myocardial CTP examinations with adenosine and dipyridamole have been used in preliminary trials.
COPD = chronic obstructive pulmonary disease; CTP = computed tomography perfusion; MDCT = multidetector computed tomography.

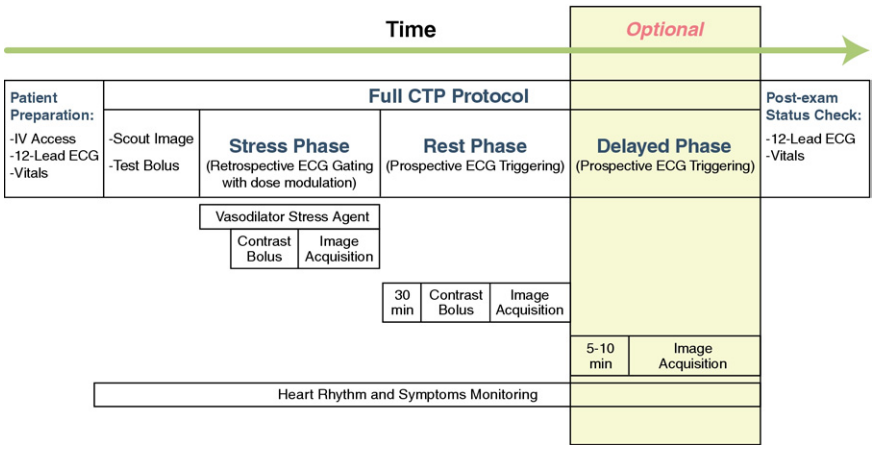

Figure 1. Full CTP Protocol

The protocol includes patient preparation and post-exam check (including an optional delayed phase acquisition (**shaded box**). All steps are as listed in sequence. Heart rhythm and symptoms are monitored throughout the entire exam. CTP = computed tomography perfusion; ECG = electrocardiogram; IV = intravenous.

contamination of contrast; however, the second scan can underestimate the presence of infarct in the myocardium if a short scan interval is used. Iodinated contrast has been shown to have similar pharmacokinetics to gadolinium-based compounds in magnetic resonance imaging (29). The contrast from the stress scan would accumulate in an area of myocardial infarct due to the slow wash-out phenomenon, leading to possible underestimation of myocardial infarction (perfusion defect during the rest scan) if the second scan is done too early after the first one (i.e., <10 min apart). A coronary CTA acquisition can be acquired simultaneously with the rest acquisition, and beta-blockers and sublingual nitroglycerin can be given to optimize the second scan. For the patient population that myocardial CTP targets, it can be argued that obtaining accurate stress phase images over rest phase is of utmost importance, because the primary aim of myocardial CTP is to detect myocardial ischemia. This importance of stress phase myocardial perfusion imaging has been illustrated in previous studies evaluating SPECT (30); going forward, it will be important to verify these findings for myocardial CTP as well. Moreover, there are subsets of patients that would benefit from a stress perfusion study first, such as patients with intermediate to high pre-test probability of CAD; patients with high calcium scores (i.e., calcium score >400); patients with known CAD; patients with prior myocardial infarct; or any other situation where simultaneous evaluation of a stenotic coronary vessel leading to ischemia is important to define revascularization options.

On the other hand, performing rest phase acquisition/CTA first could make sense in clinical practice if the decision to proceed to stress myocardial CTP would be guided by the CTA results, meaning that stress myocardial CTP would only be performed if a moderate or severe coronary stenosis would be found or if there is any nondiagnostic segment (calcified lesions or stents). The potential issues of this approach are 2-fold: first, the cross-contamination of contrast in the second acquisition (stress phase), potentially masking areas of ischemic

Table 2. Advantages and Disadvantages of Different CTP Protocol Sequences

Sequence	Advantages	Disadvantages
Stress → Rest	Better sensitivity of stress scan (ability to detect ischemia) Coronary CTA can be optimized with second acquisition by giving medications without interfering with perfusion assessment	Contrast contamination, leading to appearance of late contrast enhancement during rest acquisition (decreased sensitivity for infarct)
Rest → Stress	Ability to stop protocol after rest phase (if no or minimal disease is evident) Better sensitivity of rest scan (ability to detect infarct)	Contrast contamination, leading to appearance of late contrast enhancement during stress acquisition (decreased sensitivity for ischemia) Beta-blocker given during first acquisition can underestimate myocardial ischemia

CTA = computed tomography angiography; CTP = computed tomography perfusion.

myocardium (reversible stress perfusion defect) as illustrated in Figure 2; and second, the use of beta-blockers to optimize image quality of coronary CTA in the first acquisition could also lead to underestimation of myocardial ischemia. The first issue can be avoided by having an interval of at least 30 min between the rest and stress acquisition to allow washout of contrast from the myocardium. The second issue can be avoided if the temporal resolution of CT scanners keeps improving, alleviating the need to use beta-blockers. In summary, for future implementation of stress myocardial CTP, it may be advantageous to stratify patients into low-risk and high-risk groups. The low-risk group would undergo a rest phase scan first with the aim of ruling out CAD, whereas the high-risk group would start with the stress phase scan for detection of myocardial ischemia and then an optimized CTA/rest myocardial CTP exam with a beta-blocker and nitroglycerin can be acquired.

For the stress phase acquisition, infusion of the pharmacological stress agent is initiated (with a rate of 140 μg/kg/min for adenosine infused over 3 to 4 min and 0.56 mg/kg of dipyridamole infused over 4 to 6 min). When the pharmacological stress agent reaches its peak, 60 to 70 ml of contrast is delivered at 4 to 5 ml/s. The stress phase scan is then acquired using the previously derived timing or the trigger bolus method. The stress phase scan can be acquired using a retrospectively gated scan with ECG tube current modulation. Tube voltage of 100 kV is used for patients with body mass index of <30 kg/m^2 and 120 kV for body mass index ≥ 30 kg/m^2. Tube current can also be adopted depending on the patient's body habitus. Throughout the entire process, the patient's symptoms, heart rate, blood pressure, and ECG are closely monitored. The pharmacological stress agent is stopped immediately after the stress phase acquisition (or reversed in case of dipyridamole).

If the rest phase acquisition follows the stress phase acquisition, there should be a period of delay (at least 20 min) in order for the effects of the pharmacologic stress to resolve. Resolution of symptoms and return of heart rate to baseline can be used as a proxy to judge when the effects have resolved. For the rest acquisition, another 60 to 70 ml of contrast is again delivered at 4 to 5 ml/s; the acquisition employs similar timing as the stress acquisition. Unlike the stress acquisition, the rest acquisition is performed via prospective ECG

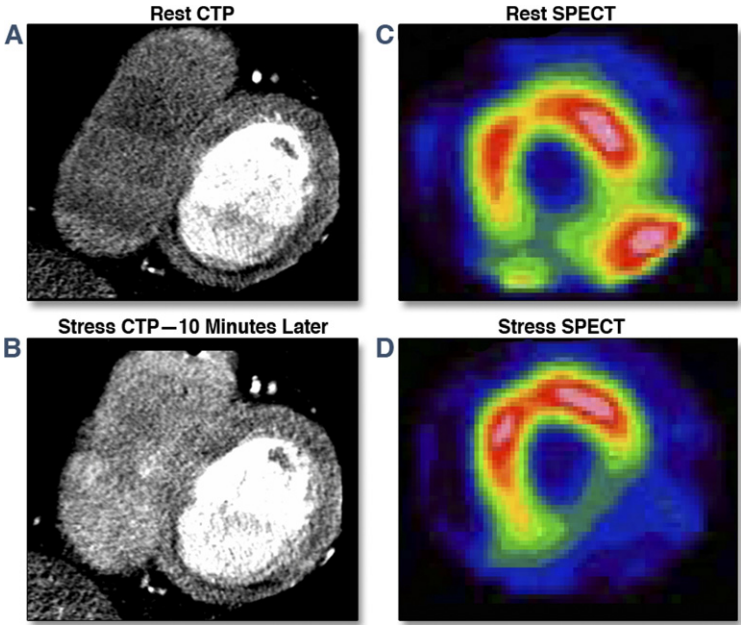

Figure 2. Contrast Contamination of Stress Acquisition Leading to a False Negative

Patient underwent a computed tomography perfusion (CTP) protocol with rest acquisition followed by stress acquisition 10 min later. **(A)** Shows the rest acquisition revealing a perfusion defect inferiorly. **(B)** Reveals a stress acquisition that is contaminated by previous contrast administration, leading to the appearance of a smaller area of defect during stress. **(C,D)** Reveal a fixed, inferior wall perfusion defect on single-photon emission computed tomography (SPECT). Although SPECT did not reveal any ischemic myocardium in this particular example, it is easy to imagine that an area of stress-induced ischemia can be missed on CTP if the stress phase acquisition is performed second. Of note, there is gastric uptake in **(C)**; however, this did not interfere with the interpretation in this case.

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triggering at mid-diastole to minimize radiation dose, but the tube voltage and current settings were similar to those used for the stress scan. This phase can be used to assess both the coronary arteries and rest myocardial CTP. Beta-blockade with intravenous metoprolol can be administered, as in the case of traditional CTA protocol, to optimize the visualization of coronary anatomy by decreasing the heart rate. Studies evaluating the feasibility of myocardial CTP have been conducted with and without the use of beta-blockers, all showing comparable results (17–19). The administration of nitroglycerin can also be used to achieve coronary vasodilation. However, it should be noted that nitroglycerin is known to affect myocardial perfusion, and thus may interfere with the accuracy of the study (31).

A third scan can be added to assess for delayed enhancement (i.e., myocardial infarct) This acquisition is performed approximately 5 to 10 min after the completion of the second (either stress or rest) acquisition. No contrast injection is needed for this phase, as it employs previously injected contrast in the stress and rest phases. The acquisition is prospectively ECG-triggered at mid-diastole of the cardiac cycle, similar to the rest phase scan. Tube voltage is set to 100 kV; tube current settings are similar to those used for the stress and rest scan. Finally, post-exam ECG and blood pressure measurements are performed to ensure patient's safety.

The necessity and the value of the delayed phase scan as part of myocardial CTP has not been well established at this point. Gerber et al. (29) illustrated the similar pharmacokinetics between iodinated contrast and gadolinium in infarcted myocardium over a decade ago. Since then, it has been shown in patients that CT delayed enhancement can be detected in infarcted myocardium, but with relatively poorer signal-to-noise and contrast-to-noise ratios (32). Blankstein et al. (18). found that delayed enhancement on CT correlated well with rest perfusion defect on SPECT as a part of comprehensive myocardial CTP protocol; however, this comparison was done only in subjects with favorable image quality. There is also additional radiation exposure to the patient, though this is relatively low (approximately 1 mSv or less) when prospective triggering and low tube voltage is used. Overall, there is not enough literature to definitively support the incorporation of a delayed phase scan as a part of myocardial CTP protocol; however, further research on the use of delayed enhancement CT for viability evaluation is needed.

Image processing and interpretation. Raw scan data from the 2 or 3 phases (stress, rest, and delayed) are reconstructed into axial image datasets at mid-diastole, using a smooth filter with slice thickness of 0.7 mm and overlap of 0.4 mm. The axial images are then used to create short-axis, 2-chamber, and 4-chamber views by multiplanar reconstruction. Thicker reconstruction (~8 to 10 mm) of average multiplanar reformation is preferred for the detection of perfusion defect. Minimum-intensity projections may be more sensitive in bringing out subtle perfusion defects; however, it is also more susceptible to increased noise and false positives (33). Maximum intensity projections are not useful, as they mask perfusion defects. Images are co-registered and read in a side-by-side fashion (see Fig. 3 for an example). Narrow window width (~100 to 200 HU) should be used centered at attenuation of around 100 HU (window level).

There is a direct relationship between the amount of iodinated contrast within the myocardium and myocardial attenuation (HU). As such, a relative difference in myocardial perfusion can be visualized as differing attenuations; areas of myocardium with decreased blood flow would have a lower attenuation—a perfusion defect. When present, a perfusion defect can usually be detected visually; confirmation with region of interest measurements can be helpful. The interpretation of perfusion defect while under stress and/or at rest (i.e., ischemia and/or infarct) in myocardial CTP is similar to the interpretation of nuclear MPI, with reversibility serving as the key distinguishing feature. A simple guide to myocardial CTP interpretation is shown in Figure 4.

For the interpretation of delayed phase acquisition, the fundamental guiding principle is the similar pharmacokinetics between iodinated contrast used in CT and the gadolinium-based contrast used in magnetic resonance. Time-dependent contrast patterns characterizing myocardial infarct have been established with both contrast agents, with first-pass hypoenhancement due to decreased contrast delivery to the infarcted region and delayed enhancement secondary to increased distribution volume and altered contrast pharmacokinetics in dead myocardial tissue (29,34).

Review of the Literature

The concept of CT examination for myocardial perfusion defect was first investigated in 1978 soon after the advent of the modality (35).

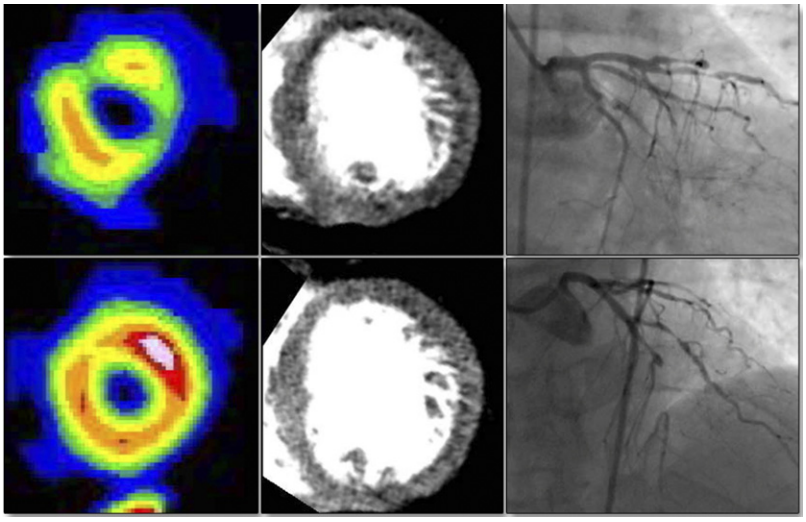

Figure 3. Comparison of CTP, SPECT, and Invasive Coronary Angiography

Shown is a 55-year-old man with history of hypertension and hyperlipidemia who presented with symptoms of substernal chest pain on exertion. SPECT myocardial perfusion imaging illustrated partially reversible anterior, anteroseptal, and lateral perfusion defect (**left panels: top** = stress, **bottom** = rest). CTP illustrates similar defects (**middle panels: top** = stress, **bottom** = rest). Upon cardiac catheterization, occlusion in the left anterior descending **(bottom right)** and significant stenosis in the left circumflex **(top right)** coronary arteries are seen. Abbreviations as in Figure 2.

However, the reliable use of CT to detect myocardial perfusion defect has only been achieved with the recent advancements in CT technology. The first attempt to use multidetector CT to characterize myocardial perfusion defects in human under stress was first explored by Kurata et al. in 2005 (36), using adenosine stress on a 16-detector multidetector computed tomography (MDCT) scanner. Although the study showed good agreement between myocardial CTP and thallium-201 myocardial perfusion scintigraphy, only 48% of coronary segments were evaluable under stress (compared with 89% at rest, $p < 0.05$), illustrating that myocardial CTP was not feasible at that time due to the limitations in the temporal resolution. Since then, numerous studies have been performed to evaluate the feasibility of stress myocardial CTP in both animal models and humans with newer generation of scanners showing improved results.

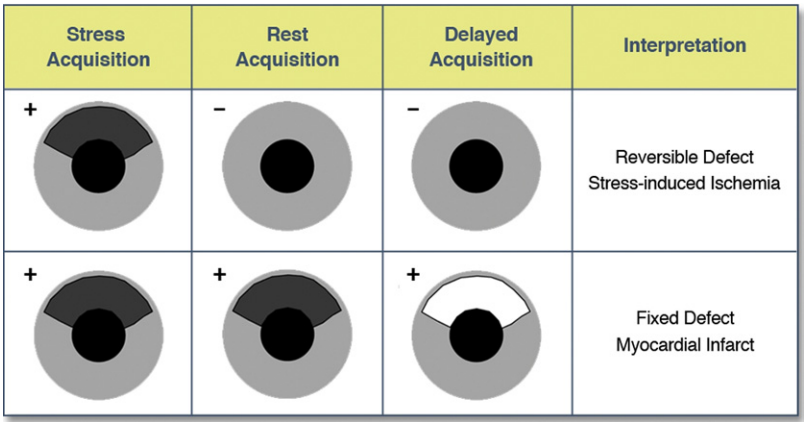

Figure 4. Basic Guide to Interpretation of CTP

A perfusion defect under pharmacological stress that reverses at rest is, by definition, stress-induced ischemia. A fixed (irreversible defect) is characteristic of myocardial infarction. Note that myocardial infarction also exhibits late contrast enhancement in a fashion similar to late gadolinium enhancement in cardiac magnetic resonance. CTP = computed tomography perfusion.

Table 3. Summary of Animal Studies Evaluating Myocardial Stress CTP

First Author, Year (Ref. #)	Animal Model	CTP Protocol	Reference Standard	Results	Conclusion
George et al., 2006 (37)	Canine (n = 8) LAD stenosis	Adenosine stress 64-detector MDCT	Microsphere MBF	Linear relationship between myocardial signal density ratio (myocardial attenuation/left ventricular attenuation)	Adenosine stress MDCT provides semi-quantitative measurements of myocardial perfusion in canine model of LAD stenosis
George et al., 2007 (38)	Canine (n = 6) LAD stenosis	Adenosine stress 64-detector MDCT	Microsphere MBF	MDCT-derived MBF strongly correlated with microspheres (R = 0.91, $p < 0.0001$)	MDCT MBF measurements using upslope and model-based deconvolution methods correlate well with microsphere MBF
Christian et al., 2010 (39)	Porcine (n = 8)	Adenosine stress 64-detector MDCT	Microsphere MBF	Significant correlation between coronary flow reserve measurements between microsphere MBF and CT ($r = 0.94$, $p < 0.0001$)	CT first-pass myocardial perfusion imaging is feasible using a simple semi-quantitative analysis which provides reasonable estimates of MBF.
Mahnken et al., 2010 (43)	Porcine (n = 10) LAD stenosis Normal control	Adenosine stress 128-detector DSCT Dynamic scan mode	—	No significant differences in CT-based MBF between the stenotic and control group at rest; however, significant difference under adenosine stress ($p = 0.0024$).	DSCT permits quantitative whole heart perfusion imaging, with ability to show hemodynamic effect of high grade coronary artery stenosis.

DSCT = dual source computed tomography; LAD = left anterior descending coronary artery; MBF = myocardial blood flow; other abbreviations as in Tables 1 and 2.

The first animal studies illustrating feasibility of myocardial CTP using MDCT were performed by George et al. (37,38) in canine models (Table 3). These studies established the semiquantitative relationship between CT attenuation and blood flow based on microsphere myocardial blood flow (MBF). Further work in a porcine model has confirmed that coronary flow reserve measurements by microsphere MBF and myocardial CTP correlate well with each other (39). In human studies, results from multiple cohorts employing different scanners and pharmacological stress agents (Table 4) seem to confirm the initial findings of animal studies. It should be noted that these initial studies are conducted at various institutions with differences in protocols and reference standards. The unifying theme, however, is that perfusion defects on myocardial CTP seem to correlate well with perfusion defects on SPECT, stenoses on quantitative coronary angiography (QCA), or both. For further details on reference standards used, refer to Table 4. George et al. (17) used adenosine as the pharmacological stress agent, beta-blockers for heart rate control, and 64-detector MDCT or 256-detector MDCT for image acquisition. The combined analysis of all patients (including both scanner types) in this study showed a per-vessel territory sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 75%, 87%, 60%, and 93%, respectively, when compared with QCA and SPECT. The potential limitations of this study are nonuniformity of protocols and use of beta-blockers, which may have blunted the degree of difference in perfusion between the ischemic and the nonischemic heart. Blankstein et al. (18) acquired myocardial CTP images under adenosine

Table 4. Summary of Human Studies Evaluating Myocardial Stress CTP

First Author, Year (Ref. #)	Scanner Type	Comparison*	Stenosis (%)†	n	mSv	Sn (%)	Sp (%)	PPV (%)	NPV (%)
George et al., 2009 (17)	64/256-MDCT	CTA/CTP vs. QCA/SPECT	>50	27	16.8 (64) 21.6 (256)	86	92	92	85
Blankstein et al., 2009 (18)	DSCT	CTP and SPECT vs. QCA	>50	33	12.7	92	67	89	75
Rocha-Filho et al., 2010 (20)	DSCT	CTA/CTP vs. QCA	>50	34	11.8	96	100	100	91
Cury et al., 2010 (19)	64-MDCT	CTP and SPECT vs. QCA	>70	36	14.7	94	75	89	86
Ho et al., 2010 (44)	2nd-generation DSCT	Dynamic CTP vs. SPECT/QCA	—	35	18.2	95	65	78	79
Ko et al., 2011 (46)	DSCT	DECT vs. CMR/QCA	—	50	—	89	76	—	—
Total			50–70	215	11.8–21.6	86–96	67–100	78–100	79–91

*Note that the study designs and reference standards vary widely. †Stenosis (%) refers to the stenosis threshold used in studies which employed QCA as a part of the reference standard. CMR = cardiac magnetic resonance; NPV = negative predictive value; PPV = positive predictive value; QCA = quantitative coronary angiography; Sn = sensitivity; Sp = specificity; other abbreviations as in Tables 1 and 3.

stress using a dual source CT scanner, which has higher temporal resolution, obviating the need for beta blockade. The comprehensive myocardial CTP protocol also uniformly included a rest and a delayed phase acquisition in all study subjects. The results showed that myocardial CTP is equivalent to SPECT in detecting coronary artery stenosis by QCA, with per-vessel territory sensitivity and specificity of 79% and 80% for myocardial CTP and 67% and 83% for SPECT, respectively (p = NS). Furthermore, the CTA obtained during the stress phase of the scan was excellent for diagnosing stenosis of 70% or more on QCA. The study also illustrated that the full myocardial CTP protocol can be done at similar radiation exposure to SPECT MPI (12.7 mSv for both). Subsequent studies based on the same cohort further confirmed the feasibility and value of myocardial CTP. Rocha-Filho et al. (20) demonstrated that adding perfusion information obtained from stress myocardial CTP to coronary CTA improves all diagnostic characteristics of CTA alone, particularly specificity and PPV. Okada et al. (40) illustrated the concordance between myocardial CTP and SPECT in the detection and evaluation of size and severity of myocardial perfusion defects at stress and at rest. In another cohort of patients, Tamarappoo et al. (41) compared the extent and severity of perfusion defects between myocardial CTP and SPECT using a 5-point scale and a total perfusion deficit score. For both methods, good agreement was achieved. Cury et al. (19) employed a different stress agent, dipyridamole, on a 64-detector MDCT scanner. Their results also demonstrated that myocardial CTP is at least equivalent to SPECT in the detection of stenosis found on QCA (sensitivity and specificity: 88% and 79% for myocardial CTP and 69% and 71% for SPECT, p = NS).

Recently introduced dual energy mode and dynamic scan mode have also been investigated for the detection of perfusion defects (42–44). Dual energy scan mode takes advantage of the fact that different materials have different spectral characteristics when penetrated by different x-ray energy levels; this allows for the mapping of iodine concentration within the myocardium—potentially reflecting the degree of myocardium perfusion (45). Initial investigation by Ruzsics et al. (42) demonstrated that dual energy computed tomography (DECT) had a sensitivity and specificity of 96% and 95% in detecting fixed perfusion defect seen on SPECT. Furthermore, DECT had a sensitivity and specificity of 88% and 89%, respectively, for the detection of reversible perfusion defect (42), although the physiological mechanism behind such a concordance remains controversial as DECT was not performed under stress in the study. Most recently, Ko et al. (46), in a study of DECT in the setting of adenosine stress, illustrated that DECT had a sensitivity, specificity, and accuracy of 89%, 78%, and 82%, respectively, for the detection of myocardial segments with perfusion defect, using stress perfusion MRI as the gold standard.

Preliminary experiences with dynamic myocardial CT perfusion imaging also showed good promise in both animal models and human patients. Mahnken et al. (43) illustrated the ability of dynamic quantitative whole-heart perfusion imaging to detect the hemodynamic effect of high-grade coronary artery stenosis in a canine model. Furthermore, in an early experience with a patient cohort, Ho et al. (44) demonstrated that stress and rest dynamic perfusion imaging can detect myocardial perfusion defect with good diagnostic accuracy when compared with SPECT MPI (per-segment sensitivity, specificity, PPV, and NPV of 83%, 78%, 79%, and 82%, respectively) and with QCA (per-segment sensitivity, specificity, PPV, and NPV of 95%, 65%, 78%, and 79%, respectively) and allows for defining time-attenuation curves with the potential for quantification of myocardial blood flow. However, it should be noted that the radiation dose for this protocol (around 20 mSv) is much higher than static myocardial CTP. Furthermore, the use of qualitative SPECT as a reference standard is suboptimal for such analysis (47).

Study limitations. Myocardial CTP as a modality still has a number of limitations, some of which will eventually be overcome as CT technology improves. There are a few CT-related artifacts that the physician should recognize and try to minimize when performing and interpreting myocardial CTP, namely beam-hardening and motion artifacts.

Beam hardening is a phenomenon that occurs when x-ray beams pass through objects of high density, leading to a selective attenuation of lower-energy beams and increased mean energy of the remaining beams. The resulting appearance is a hypoenhanced region that may mimic areas of true perfusion defect. There are a few characteristics that physicians can use to help identify beam-hardening artifacts. The hypoenhanced region is usually triangular in shape, appears to originate from the region of high attenuation next to it, and does not conform to vascular territories (37). A particularly common location includes the basal inferolateral wall, due to proximity to the descending aorta with iodinated

Table 5. Tips to Distinguish Artifacts From True Perfusion Defects

Artifacts	Tips
Motion	Does not correspond to a vascular territory Does not correspond with wall motion abnormality in the same segment Does not persist across different phases of the cardiac cycle
Beam-hardening	Same as motion artifact above Perfusion defect in early arterial phase due to the presence of high dose of dense contrast in the ventricle Perfusion defect in the basal inferolateral wall due to the proximity of the dense spine and contrast in the descending aorta Perfusion defect that is triangular in shape, originating from the region of high attenuation in the proximity

contrast and dense vertebral bodies. Attempts to develop an algorithm to minimize beam-hardening artifacts are ongoing, with the use of iterative reconstruction.

Myocardial CTP is also prone to motion artifacts similar to coronary CTA, particularly during the stress phase acquisition, due to the increased heart rate. Cardiac motion during the acquisition leads to hypoenhanced areas that can mimic true perfusion defects. Motion artifacts are becoming less of an issue as the temporal resolution of CT continues to improve. Moreover, by assessing multiple phases of the cardiac cycle, one might be able to differentiate a true perfusion defect from an artifact as the perfusion defect will persist and the artifact will disappear or change in location. Regional wall motion abnormalities can also be detected associated with true perfusion defects. Table 5 lists helpful tips in distinguishing artifacts from true perfusion defects.

Conclusions and Future Directions

The feasibility of stress myocardial CTP as a clinical entity has thus far been evaluated in animal models and single-center prospective patient cohort studies as listed in Tables 3 and 4. The initial results using 64-MDCT and newer scanners have been promising, showing that myocardial CTP has comparable diagnostic characteristics to SPECT MPI in the detection of myocardial perfusion defects. Furthermore, myocardial CTP protocol allows for the simultaneous acquisition of coronary anatomy and myocardial perfusion, and a combined CTA/CTP protocol has been shown to have better diagnostic characteristics than CTA alone. The radiation exposure in such protocols is similar to that of a traditional SPECT MPI exam; the radiation exposure is also likely to decrease as CT technology advances (18). These data suggest that myocardial CTP has the potential to become a robust clinical tool for the evaluation of chest pain patients. However, it should be noted that the modality is in a very early stage of development. Published studies are composed only of single-center preliminary experiences. All evaluated cohorts thus far are based on a referral population of patients with intermediate to high pre-test probability of CAD and patients referred to other tests such as SPECT MPI and cardiac catheterization. Furthermore, no standardized protocol currently exists for myocardial CTP studies as the feasibility studies all utilized varying protocols. More research is needed in order to further define, optimize, and validate the modality. Particularly, a prospective multicenter, multivendor trial evaluating the diagnostic characteristics of myocardial CTP in a wider patient population is needed to confirm the findings of these promising preliminary trials in order to establish myocardial CTP as a viable clinical option.

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